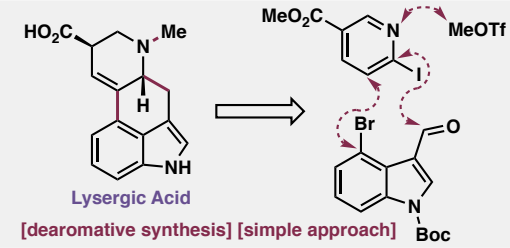
A Concise and Malleable Synthesis of (±)-Lysergic Acid

Brian J. Knight†, Ryan C. Harbit†, and Joel M. Smith*

Department of Chemistry and Biochemistry, Florida State University, 95 Chieftan Way, Tallahassee, FL 32306

Supporting Information Placeholder

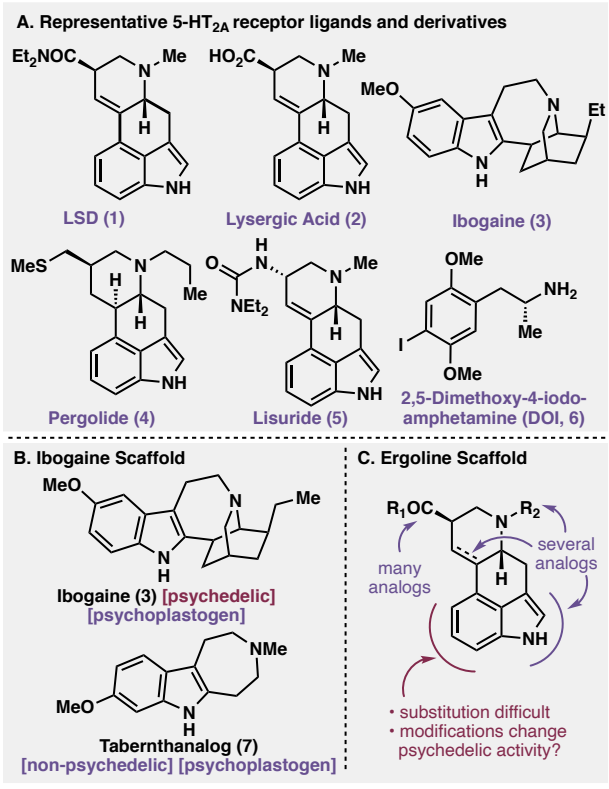


ABSTRACT: This Letter describes a concise synthesis of lysergic acid from simple aromatic precursors. The successful strategy relies on the coupling, dearomatization, and cyclization of a halopyridine with a 4-haloindole derivative in 6 total synthetic steps from commercial starting materials. In addition to highlighting the advantages of employing dearomative retrosynthetic analysis, the design is practical and anticipated to enable the synthesis of novel neuroactive compounds.

Since Hofmann's discovery of lysergic acid diethylamide (LSD, **1**) in 1938, the medicinal wonders of this natural product derivative have proven both intriguing and controversial.[1,2] For instance, Sandoz Laboratories heralded LSD as "a cure for everything" in the 1940s, while US congress, in partial response to counter-culture of the 1960s, made its possession and use illegal in 1968.[3] Despite this ongoing debate, some ergoline derivatives such as pergolide (**4**)[4] and lisuride (**5**)[5] have found their way to the clinic for the treatment of Parkinson's disease and migraines. These ergolines, in addition to the psychedelics dibogaine (**3**) and 2,5-dimethoxy-4-iodoamphetamine (**6**) are ligands for the 5-HT_{2A} GCPR, a key receptor responsible for many downstream neuropharmacological phenotypes.[6] Because of LSD's therapeutic potential, several X-ray crystallographic structures have recently been obtained that enable the design of 5-HT_{2A} ligands capable of novel neuropharmacology.[7–9] Thus, we maintained that a practical synthesis of diverse LSD (**1**) derivatives would aid this burgeoning realm of biomedical research.[10,11]

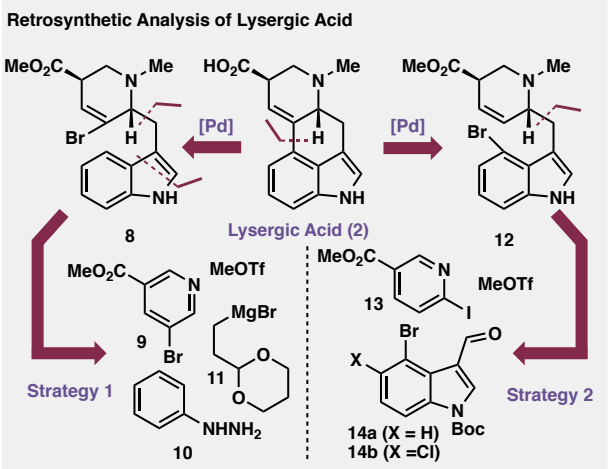
Recently, Olson and coworkers identified that **7**, bearing a simple change substitution of the benzenoid ring of ibogaine (**3**), showed similar psychoplastogenic effects without the psychedelic effects in **3** (Figure 1B). [12] This intriguing discovery, coupled with another study on dimethyltryptamine analogs,[13] spurned our curiosity regarding similar substituents effects on the ergoline scaffold, which have been largely unexplored in the neuropharmacology of LSD.[14,15] While many ergoline derivatives have been accessed from natural isolates (e.g. **4**, **5**) via functionalization at chemically "available" sites (See Figure 1C), we hypothesized that benzenoid substitution would require a short and modular synthesis in order to understand the potentially analogous substituent effects observed in **7**.

Figure 1



(A) 5-HT_{2A} ligands (B) psychoplastogenic tryptamines (C) Ergoline scaffold amenable for chemical modification.

Figure 2

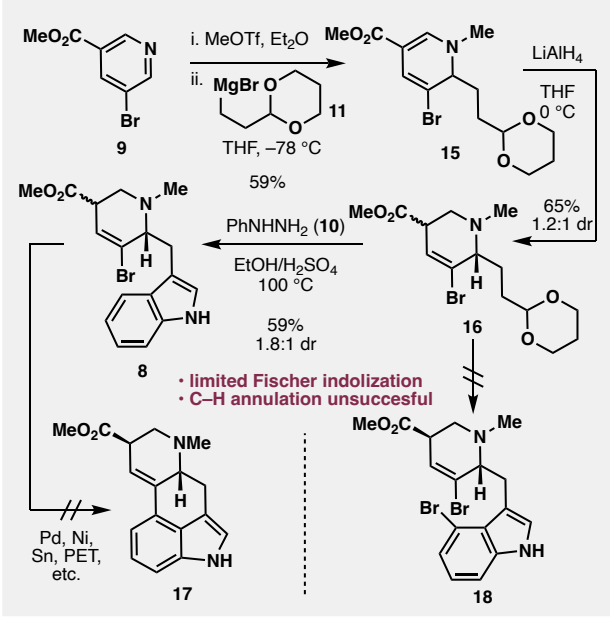


Lysergic Acid Retrosynthetic Analyses

Targeting lysergic acid (**2**), the synthetic precursor to LSD, was a starting point towards synthesizing and validating any psychoactive LSD derivatives.[16,17,26–35,18–25] This includes the controversial short synthesis of **2** reported by Hendrickson[25] which was later disputed by both Nichols[36] and Boger.[37] Overall, two retrosynthetic strategies were considered to allow quick access to **2**. In a first strategy, it was envisioned that the natural product would arise from a late-stage Pd-catalyzed annulation of vinyl bromide **8** via C-H vinylation of the C4 position of the pendant indole heterocycle.[38] Intermediate **8** would be the product of a Fischer indolization reaction with phenylhydrazine (**10**) and a tetrahydropyridine (not shown) synthesized from a dearomatization and reduction sequence between pyridine **9** and Grignard reagent **11**.[39] If the first strategy were inoperable (*vide infra*), it was also hypothesized that a Heck reaction could forge the scaffold of **2** from bromoindole **12**.[32–34] This tetrahydropyridine would be ultimately derived from a pyridinium reduction following the coupling of iodide **13** and aldehyde **14**, both of which are commercially available. While both approaches included attractive modularity and brevity, strategy 1 was pursued first.

Scheme 1 depicts efforts towards **2** implementing strategy 1. Starting from bromopyridine **9**, methylation of the pyridine nitrogen with MeOTf generated an intermediate *N*-methylpyridinium that was trapped with Grignard reagent **11** to produce dihydropyridine **15** as the major regioisomer in a 2.6:1 C6/C4 ratio and in 82% overall yield (59% of **15**). From our previous studies on the regiochemistry of pyridinium dearomatizations, we predicted the combined directing effect of the ester and bromide substituents would increase addition at C6.[39] Next, reduction of the vinylogous carbamate in **15** with $LiAlH_4$ proceeded in 65% yield to deliver a 1:1 mixture of diastereomers of acetal **16**. This mixture was deemed inconsequential for the synthesis of **2**, as the alpha center to the ester is thermodynamically resolvable upon construction of the ergoline framework.[20,34] Acetal **16** was then treated with phenylhydrazine (**10**) and a 4% H_2SO_4/EtOH mixture at elevated temperature to afford indole **8** in 59% yield (1.8:1 dr). Notably, this Fischer indolization reaction was attempted with a variety of other phenylhydrazine derivatives that gave no observable indole products. This unexpected result impeded abilities to generate modified downstream intermediates (e.g. **18**) en route to **2**.

Scheme 1

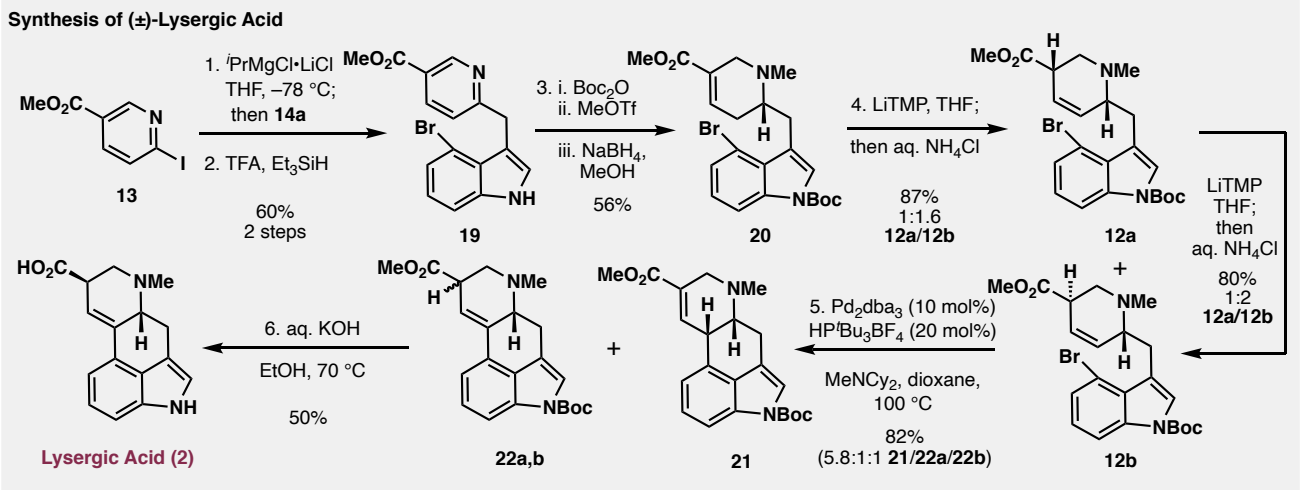


First-Generation Approach to Lysergic Acid

With **8** in hand, our efforts focused on the C–H annulation to close the last six membered ring found in lysergic acid (**2**). Initially, following prior precedent for this kind of transformation,[38] the only observable product was annulation at the C2 position of the indole heterocycle (not shown). Attempts to sterically deter this undesired cyclization were thwarted by an inability to properly functionalize or protect the indole nitrogen under basic conditions. Presumably, this was due to the base sensitivity of the tetrahydropyridine ring found in **8**, where attempts to deprotonate the indole nitrogen resulted in non-productive decomposition pathways.[40] Further efforts to effect annulation of the vinyl bromide using Ni-catalysis or radical propagation[39,41] (e.g. PET, Bu_3SnH and AIBN) also largely resulted in hydrodebromination of **8**. Additionally, while a reductive coupling tactic might have been possible through an intermediate such as **18**, the Fischer indolization of **16** was only operable with phenylhydrazine (**10**), disallowing access to benzenoid-functionalized indole congeners of **8**. With an unproductive annulation tactic and a limited Fischer indolization reaction, the second strategy outlined in Figure 1 became more attractive for the synthesis of **2**. As the same final ring-closing strategy would be needed, a tactical change in the placement of the halogen would likely allow for a more competent and reliable annulation.

Scheme 2 outlines the forward implementation of the second retrosynthetic strategy towards **2**. Starting from iodopyridine **13**, magnesium–halogen exchange[42,43] generated a heterocyclic nucleophile that was trapped with commercial aldehyde **14** to afford an intermediate alcohol (not shown) in 85% yield. Exposure of this intermediate to Et_3SiH and TFA cleaved the Boc protecting group and reduced the benzylic alcohol to generate indole **19** in good yield on gram scale. The next step in the synthesis involved the key reductive dearomatization of the pyridine to a tetrahydropyridine. In the event, Boc protection of **19** followed by *in situ* methylation of the

Scheme 2



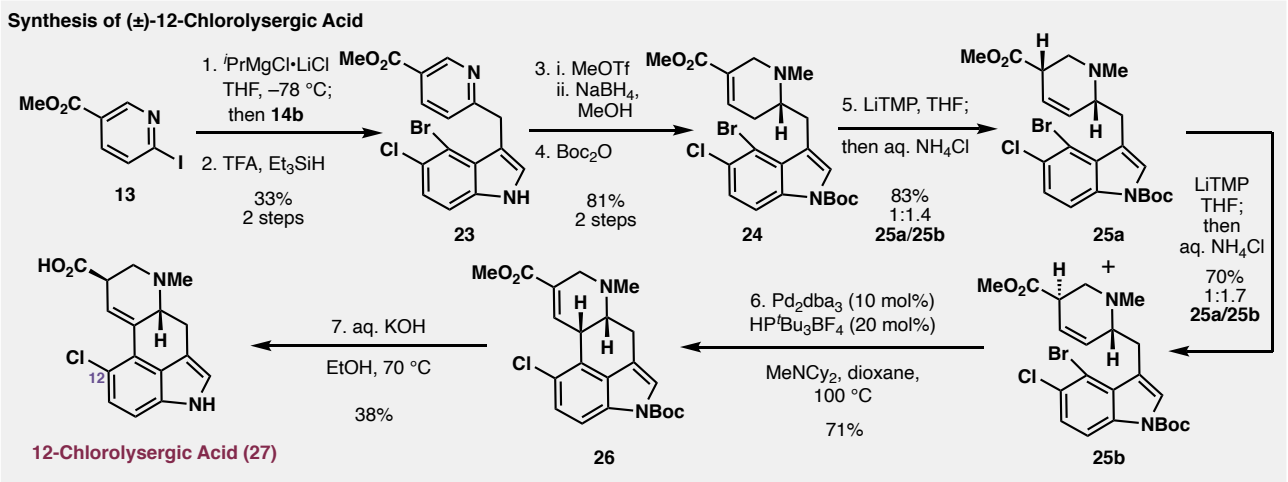
Second-Generation Approach to Lysergic Acid

pyridine nitrogen resulted in an intermediate pyridinium salt. This unisolated intermediate was treated with $NaBH_4$ to smoothly generate dihydropyridine **20** in 56% yield. Isomerization of the enoate with LiTMP gave a 1:1.6 diastereomeric mixture of **12a** and **12b**, of which the latter was poised for the key Heck annulation.[31,34] Conveniently, **12a** can be converted to **12b** upon its re-exposure to the isomerization conditions with an identical diastereomeric outcome. Treatment of **12b** with a catalytic amount of Fu's Pd^0 complex[44] (generated *in situ*) allowed for facile generation of **21** in excellent yield along with **22a** and **22b**, two diastereomeric alkene isomers, in a 5.8:1:1 ratio, respectively. While similar transformations have been reported,[31,33,34] low yields and/or stoichiometric amounts of Pd have been required to effect this annulation, attesting to its challenging implementation. The stereochemistry of the center alpha to the ester in **12b** was crucial to the success of this reaction, allowing for *syn*-beta-hydride elimination to proceed following migratory insertion of the putative arylpalladium(II) intermediate. Finally, saponification and isomerization of the mixture of **21**, **22a**, and **22b** was executed as previously reported to generate lysergic acid (**2**) in 52% yield.[20]

The successful generation of **2** spurned our expansion of this synthetic platform towards the generation of new lysergic acid derivatives with novel benzenoid substitution. As a proof of principle, we adapted our synthesis to the generation of 12-chlorolysergic acid. Starting from iodopyridine **13**, magnesium halogen exchange followed by addition to aldehyde **14b** (See Supporting information for synthesis) resulted in an intermediate benzylic alcohol that was reduced to give biaryl **23** in modest yield over 2 steps. Methylation and reduction of the intermediate was followed by Boc protection of the indole proceeded in 81% yield (over 2 steps) to afford **24** . This intermediate was subjected to base-mediated isomerization to give a 1:2 ratio of **25a**/**25b** in 83% yield. The minor undesired isomer (**25a**) could again be recycled to afford higher quantities of **25b**, which proceeded through the Heck cyclization in excellent yield to generate a enoate **26** in 57% yield. Hydrolysis of this mixture gave 12-chlorolysergic acid (**27**) in good yield.

In conclusion, concise syntheses of lysergic acid (**2**) has been accomplished in 6 steps and 12% overall yield from commercially available materials (**13** and **14**). Central to the efficiency of this approach was the strategic and redox-economic utilization of heteroaromatic starting materials as functionalized precursors to the ergoline core. While this strategic approach was initially thwarted by an insurmountable tactical conundrum, the inversion of polar synthons enabled the con

Scheme 3



Synthesis of 12-chlorolysergic acid

struction of the final tetracyclic core. Furthermore, the synthesis of 12-chlorolysergic acid was accomplished through adaptation of the successful second-generation approach. We contend that this modular platform will enable the synthesis and investigation of efficacious psychoplastogenic LSD derivatives valuable to drug discovery and psychotherapy. We assert that the novel molecular space unlocked by this synthetic blueprint holds great promise for the increased utilization of psychedelics and their derivatives as new neuropharmacological treatments.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Supporting Information (PDF)

AUTHOR INFORMATION

Corresponding Author

* Email: smith@chem.fsu.edu

Present Addresses

Notes

† These Authors contributed to the work equally.

The authors declare no competing financial interest.

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